258 Dose finding for the inhalational tobramycin therapy using the new diaphragm nebulizer I-neb® AAD® System CF

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The new vibrating mesh technology nebulizer I-neb® AAD® System CF may offer improvements for the inhalation of anti-pseudomonas therapy for patients with Cystic Fibrosis (CF). Adaptive Aerosol Delivery (AAD) technology results in a pre-set dose of medication being delivered to the lung. AAD delivers drug during the first 50–80% inhalation only and the amount of aerosol delivered during each inhalation phase is dependent upon a patients breathing pattern which is being analysed throughout their treatment. The amount of medication is adjusted to the depth and duration of inspiration. With a residual volume of less than 0.1 ml, an efficiency of 90% and a 60% fraction of lung deposition (healthy volunteers) the inhalation therapy is more efficient, may possibly be more cost-saving and may be done in an acceptable time. The I-neb® AAD® System CF was tested first for the inhalation of Tobramycin with Gernebcin® 80 mg/2 ml (n = 12). Blood serum levels were compared with levels after inhalation with compressor and other diaphragm nebulizers and showed that less medication was needed with I-neb to achieve higher serum levels compared to the other nebulizers (0.5 µg/ml). This is due to improved efficiency and delivery characteristics of I-neb. A similar Investigation using a higher dose (160 mg/2 ml) to determine the optimal applicated dose may offer a further saving potential. International data refers to necessary serum levels of 1 µg/ml 1 h after inhalation. Our current data suggests a required dose of 94 mg, resulting in an inhalation time of about 12 min. and reduced medicine consumption.
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259 In vitro characterization of BRAMITOB (inhaled tobramycin 300 mg/4 ml) with next generation nebulisers

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Aim: Nebulisation of inhaled drugs has improved in the past years due to development of new generations of nebulisers, characterized by greater efficiency, portability and shorter nebulisation times. These achievements may improve quality of life and adherence to therapy in cystic fibrosis (CF) patients. Aim of this study was to compare in vitro performance of 4 devices [PARI TurboBOY N LC PLUS (LC), PARI eFlow Rapid (eF), Optineb-ir (Op) and Akita LC Star (Ak)] when nebulising 4 ml of BRAMITOB, a new formulation of inhaled tobramycin developed by Chiesi Farmaceutici.
Methods: By means of a Next Generation Impactor, the aerodynamic particle size distribution was studied evaluating the mass median aerodynamic diameter (MMAD) and fine particle fraction (FPF). Moreover, the Delivered Dose (DD) and the duration of nebulisation were measured.
Results: The MMAD was lowest with Ak, whereas higher with eF, LC and Op (2.7 µm, 4.1, 4.8 and 5.5 µm respectively). The FPF was higher with Ak and eF (77.3% and 66%) and lower with LC and Op (50.4% and 44.2%). The DD was similar with eF, LC and Op (86, 81.6 and 87.9 mg) but was much higher with Ak (147.2 mg). Nebulisation time was lowest with eF (5.5 min) followed by LC and Op (7.4 and 9.9 min respectively), whereas much longer with Ak (24.3 min).
Conclusions: Optineb-ir and eFlow Rapid are characterized by an aerodynamic particle size distribution and a delivered dose similar to that of PARI TurboBOY N LC PLUS, which is the device used in the clinical trials conducted with BRAMITOB. However, small differences, such as those observed in the nebulisation time, may represent an important feature when considered in the daily therapies that CF patients undergo.

260 Increased efficiency from the I-neb® AAD® System compared with a conventional jet nebulizer

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Introduction: The I-neb® Adaptive Aerosol Delivery (AAD®) System has been developed to deliver precise, reproducible doses of aerosol into inhalation. We used a model based on published in vivo data [1] to predict the lung doses from a conventional jet nebulizer (LC Plus) and the I-neb AAD System using various fill volumes. An in vitro test was used to verify the delivered doses from both nebulizers.
Methods: An LC Plus nebulizer was filled with 2 mL salbutamol (5 mg/2.5 mL) and run dry using the CEN 500 mL simulated breathing pattern. Delivered dose was collected on a filter, and analyzed using HPLC. This was repeated in triplicate for 2.5, 3, 4 and 5 mL fill volumes. These tests were repeated using an I-neb device with equivalent fill volumes, calculated from the model.
Results: As shown in Table 1, the predicted lung dose for the I-neb device approximated the predicted lung dose for the LC Plus nebulizer. The relationship between I-neb device and LC Plus nebulizer fill volumes was described by the equation $\text{I-neb}_{\text{fill}} = 0.3586(\text{LC Plus}_{\text{fill}}) - 0.3034$.
Conclusion: The I-neb AAD System required less drug to deliver an equivalent lung dose compared to a conventional jet nebulizer.

Table 1: Fill volumes and calculated lung doses for I-neb AAD System and LC Plus nebulizer

LC Plus fill volume (mL)	2.0	2.5	3.0	4.0	5.0
LC Plus delivered dose (µL)	429	732	892	1370	1836
Predicted lung dose from LC Plus (µL)	202	344	419	644	863
I-neb fill volume (mL)	0.42	0.65	0.76	1.12	1.47
I-neb delivered dose (µL)	333	577	691	1034	1359
Predicted lung dose from I-neb device (µL)	210	364	435	651	856

Reference(s)

[1] Williams K, et al. Pediatr Pulm. 2007; Suppl 30:355–356.

261 Precise dosing of five drugs commonly used by patients with cystic fibrosis using the I-neb® AAD® System

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The I-neb® Adaptive Aerosol Delivery (AAD®) System has been designed to deliver precise doses of drug to the patient. The delivered volume is determined either by the volume of the metering chamber, or by the volume metered into the medication chamber. We tested the capability of the I-neb AAD System to deliver precise doses of the five inhaled medications most commonly used by patients with cystic fibrosis (CF). Three I-nebs for each drug tested were connected via a filter to a Harvard pump set to generate the CEN simulated breathing pattern. For tobramycin 1.5 mL was metered into the medication chamber, a metering chamber of delivery volume 0.5 mL was used for hypertonic saline and 0.3 mL metering chambers were used for the three other drugs. The expected delivered dose (DD) was calculated by multiplying the metering chamber delivery volume by the drug concentration. The actual DD was assessed using a bioassay for colistimethate sodium, HPLC for tobramycin and dornase alfa, spectrophotometry for salbutamol, and ion analysis for hypertonic saline. Tests were performed in triplicate for each device/drug combination.
See Table 1 for results. The actual DD approximated the expected DD for each of the drugs.
Precise doses of colistimethate sodium, dornase alfa, tobramycin, hypertonic saline and salbutamol sulphate can be delivered into simulated breathing by the I-neb AAD system.

Table 1. Delivered dose from the I-neb AAD System for 5 drugs used by patients with CF

Drug	Metering chamber delivery volume	Drug concentration	Expected DD	Actual DD	(SD)
Colistimethate sodium	300 µL	1 MIU/1 mL	300 kIU	324.9 kIU	(15.8 kIU)
Dornase alfa	300 µL	1 mg/1 mL	300 µg	283.3 µg	(10.9 µg)
Tobramycin	1400 µL	60 mg/1 mL	84 mg	75.9 mg	(6.6 mg)
Hypertonic saline	500 µL	70 mg/1 mL	35 mg	35.9 mg	(0.6 mg)
Salbutamol sulphate	300 µL	2.0 mg/1 mL	600 µg	605.1 µg	(10.1 µg)